# Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK

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Abstract: AIMS: The purpose of this study was to evaluate the cost-effectiveness of iron repletion using intravenous (i.v.) ferric carboxymaltose (FCM) in chronic heart failure (CHF) patients with iron deficiency with or without anaemia. Cost-effectiveness was studied from the perspective of the National Health Service in the UK. METHODS AND RESULTS: A model-based cost-effectiveness analysis was used to compare iron repletion with FCM with no iron treatment. Using data from the FAIR-HF trial and publicly available sources and publications, per patient costs and clinical effectiveness of FCM were estimated compared with placebo. Cost assessment was based on study drug and administration costs, cost of CHF treatment, and hospital length of stay. The incremental cost-effectiveness ratio (ICER) of FCM use was expressed as cost per quality-adjusted life year (QALY) gained, and sensitivity analyses were performed on the base case. The time horizon of the analysis was 24 weeks. Mean QALYs were higher in the FCM arm (difference 0.037 QALYs; bootstrap-based 95% confidence interval 0.017-0.060). The ICER of FCM compared with placebo was €4414 per QALY gained for the FAIR-HF dosing regimen. Sensitivity analyses confirmed the base case result to be robust. CONCLUSION: From the UK payers' perspective, managing iron deficiency in CHF patients using i.v. FCM was cost-effective in this analysis. The base case ICER was clearly below the threshold of €22 200-€33 300/QALY gained (£20 000-£30 000) typically used by the UK National Institute for Health and Clinical Excellence and proved to be robust in sensitivity analysis. Improved symptoms and better quality of life contributed to this result.

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# Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial – an analysis for the UK

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**ABSTRACT**

**Aims**

To evaluate the cost-effectiveness of iron repletion using intravenous (i.v.) ferric carboxymaltose (FCM) in chronic heart failure (CHF) patients with iron deficiency with or without anaemia. Cost-effectiveness was studied from the perspective of the National Health Service in the United Kingdom (UK).

**Methods and Results**

A model-based cost-effectiveness analysis was used to compare iron-repletion with FCM to no iron treatment. Using data from the FAIR-HF trial and publicly available sources and publications, per-patient costs and clinical effectiveness of FCM were estimated compared to placebo. Cost assessment was based on study drug and administration costs, cost of CHF treatment and hospital length of stay. The incremental cost-effectiveness ratio (ICER) of FCM use was expressed as cost per quality-adjusted life year (QALY) gained and sensitivity analyses were performed on the base case. Time horizon of the analysis was 24 weeks.

Mean QALYs were higher in the FCM arm (difference 0.037 QALYs; bootstrap-based 95% confidence interval 0.017-0.060). The ICER of FCM compared to placebo, was €4’414 per QALY gained for the FAIR-HF dosing regimen. Sensitivity analyses confirmed the base case result to be robust.

**Conclusion**

From the UK payers’ perspective, managing iron deficiency in CHF patients using i.v. FCM was cost-effective in this analysis. The base case ICER was distinctly below the threshold of €22’200-33’300/QALY gained (£20'000-30‘000) per QALY gained, typically used by the UK National Institute of Clinical Excellence and proved to be robust in sensitivity analysis. Improved symptoms and better quality of life contributed to this result.

**KEYWORDS**

chronic heart failure; anaemia; iron-deficiency; cost-effectiveness analysis; health care costs

## INTRODUCTION

Chronic heart failure (CHF) patients are often limited in their daily activities. Frequently reported symptoms are fatigue and dyspnoea, but also impaired physical working capacity, exhaustion, susceptibility to stress, and decreased mental and cognitive performance.[1, 2] Anaemia and iron deficiency are common findings in HF patients and may partially explain these symptoms. Anaemic HF patients are at risk of increased mortality, number of hospitalisations and levels of natriuretic peptides and reduced exercise capacity and impaired quality of life (QoL). [3] Factors (e.g. renal dysfunction, haemodilution and drugs) present in HF can contribute to the development of anaemia. [3] A recent study found profound and general bone marrow dysfunction in CHF patients, another factor contributing to anaemia.[4] Iron plays a key role in the uptake, transport and storage of oxygen, which in CHF is often insufficiently supplied to the body. Iron deficiency in HF patients can exacerbate chronic diseases, affects erythropoiesis and oxidative and immune mechanisms.[3] In recent years, clinical research increasingly focused on iron therapy and administration of erythropoiesis-stimulating agents (ESAs) as treatment strategies for anaemia and iron deficiency in CHF patients.[5] Intravenous (i.v.) iron repletion with ferric carboxymaltose (FCM) has been shown to improve symptoms and QoL in patients with CHF.[6-8] FAIR-HF (see Appendix I), a randomised, double-blind, placebo-controlled trial (n=459) studied clinical and quality of life benefits of treatment with ferric carboxymaltose (FCM), an i.v. iron preparation, of iron deficient CHF patients with New York Heart Association (NYHA) class II or III, a left ventricular ejection fraction of 40% or less (for patients in NYHA class II) or 45% or less (for patients in NYHA class III), a haemoglobin level at the screening visit between 9.5 g/dl and 13.5g/dl and iron deficiency.[9] Causes of heart failure in FAIR-HF patients were predominantly ischaemic (FCM n (%) 245 (80.6); Placebo 123 (79.4)).[6] Primary and

secondary end points included NYHA functional class change from baseline and European Quality of Life-5 Dimensions (EQ-5D, EuroQol Group, Rotterdam, The Netherlands) questionnaire-based health-related quality of life (HRQoL).[10] The FAIR-HF trial showed significantly better NYHA class changes from baseline in the FCM group compared with placebo and FCM resulted in improved HRQoL (increased EQ-5D visual analogue scale (VAS) score change from baseline).[6] This study evaluated the cost-effectiveness of iron repletion using i.v. FCM in CHF patients, from the perspective of the National Health Service (NHS) in the UK.

## METHODS

We performed a model-based cost-effectiveness analysis comparing a strategy of iron-repletion with FCM with a standard strategy of no iron treatment in iron-deficient patients with or without anaemia. These strategies were generally equivalent to the strategies investigated in the FAIR-HF trial.[9] Cost differences between the treatment strategies were also modelled and are reported in the results section. A decision-tree model was used to facilitate sensitivity analysis. It allowed for performing deterministic as well as probabilistic sensitivity analyses.

The population basis for the clinical model inputs consisted of the 459 patients with NYHA functional class II and III at baseline, which formed the intention-to-treat [ITT] population of the FAIR-HF trial. Baseline characteristics are shown in Table 1. The FAIR-HF trial did not include British patients but was mostly performed in European countries (including Russia and Ukraine) with a predominantly caucasian population. Therefore the authors assume that clinical study results in a British population would not differ significantly from those of the actual trial.

Table 1. Baseline demographic and clinical characteristics of the FAIR-HF intention-to-treat population, according to study group.

| Variable | Ferric Carboxymaltose (N = 304) | Placebo (N = 155) |
|---|---|---|
| Age — years | 67.8±10.3 | 67.4±11.1 |
| Female sex | 159 (52.3) | 85 (54.8) |
| NYHA class | | |
| II | 53 (17.4) | 29 (18.7) |
| III | 251 (82.6) | 126 (81.3) |
| Left ventricular ejection fraction — % | 31.9±5.5 | 33.0±6.1 |
| Laboratory measurements | | |
| Haemoglobin — g/litre * | 119±12.6 | 119.5±13.8 |
| Serum ferritin — µg/litre | 52.5±54.5 | 60.1±66.5 |
| Transferrin saturation — % | 17.7±12.6 | 16.7±8.4 |

Data presented are mean value ± SD or number (%) of patients. Values were calculated from the study data by the authors. In the FAIR-HF trial a 2:1 randomisation was used.[9]

* Due to missing values, the N for haemoglobin are 298 (FCM) and 153 (Placebo)

µg, micrograms; g, gram; NYHA, New York Heart Association

In FAIR-HF, patients were randomly assigned to receive either FCM or placebo (normal saline). During a correction phase, patients received weekly injections until iron repletion were fulfilled.[6] The total iron dose required for iron repletion was calculated at baseline using the Ganzoni formula.[6] FCM was administered as an i.v. bolus injection of 4 ml equivalent to 200 mg of iron until repletion was achieved. Subsequently, during a maintenance phase, an injection was given every 4 weeks. Patients were assessed for NYHA functional class and quality of life at baseline and weeks 4, 12 and 24. Quality of life was represented by health state utilities measured with the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D). The EQ-5D is an instrument designed for self-completion by respondents. The instrument comprises two parts: Firstly, respondents report their health status according to a five-

dimensional classification (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension is represented by a three level ordered category item, which leads to a total of 243 possible health ratings that are valued using the standard United Kingdom time trade-off value set. Secondly, the respondents record their self-perceived health status using a graduated visual analogue scale (VAS), with grades from 0 to 100. The EQ-5D is a generic QoL instrument which has been validated and shown to be sensitive, internally consistent, and reliable in the general population and different patient groups.[11-13]

In the cost-effectiveness analysis, available outcome measures for the different strategies assessed, were (1) cost, (2) effectiveness, expressed as the number of quality-adjusted life years (QALYs) accrued during the study period and (3) incremental cost-effectiveness ratio (ICER), expressed as cost per QALY gained. Costs are reported in Euros (€) and British Pounds (£). For the conversion of £ to € an exchange rate of 1.11 was used (mean exchange rate for 2009; source: www.oanda.com). Costs and benefits were not discounted given the short time horizon of the study period. Where necessary, cost information was inflation-corrected using the PSSRU's Unit Costs of Health and Social Care inflation indices.[14] Costs borne by the patient and society as a whole were not incorporated, as they are not relevant from the NHS perspective.

The time horizon of the analysis was 24 weeks, corresponding to the duration of the FAIR-HF trial. Extrapolation of the time horizon to a longer term, e.g. lifelong time horizon, was not considered adequate as the FAIR-HF trial provides no information on longer-term survival or other long-term effects. In the FAIR-HF trial the rates of death, hospitalization, and serious or any adverse events were similar in the two study groups.[6]

Two approaches to cost estimation were used, as there was no detailed medical resource use information available, that would have allowed to directly assess direct

medical costs. (1) In the base case analysis, only CHF-related hospitalization costs were taken into account. (2) In a univariate sensitivity analysis, the costs of CHF treatment were estimated using cost proportions observed for patients in different NYHA classes.

In both approaches, UK FCM costs and UK FCM administration costs[15, 16] were additionally taken into account. Costs for adverse events were not included because there weren't any clinically relevant differences between the FAIR-HF study arms. Table 3 provides an overview of the different approaches used in the analysis. All data derivations from the FAIR-HF raw data were performed by the authors and checked for consistency with the publication by Anker et al.[6] where applicable.

**Model inputs**

*Clinical data.* EQ-5D questionnaire (base case analysis) and visual analogue scale (VAS; sensitivity analysis) results from FAIR-HF,[6] measured at baseline and at weeks 4, 12 and 24, were converted into utility values as described above. QALYs were calculated by multiplying these utilities with the appropriate time periods for each individual. In order to achieve this, any changes in utility were assumed to occur in the middle of the periods defined by the assessment time points. Observations with missing values were imputed with the value of the last observation (last observation carried forward, LOCF), as was done in the FAIR-HF main clinical publication. Effectiveness was assessed as the number of QALYs accrued during the study. Clinical response to treatment, measured by change in NYHA class, was also assumed to be the same as in FAIR-HF.

*Medical resource use*. In the base case analysis medical resources taken into account were drug (FCM), FCM administration and hospitalization for CHF (Table 2). Concerning drug usage, there was no wastage as FCM vials were fully administered

in each case. Hospitalisation costs were determined by multiplying UK-based hospital length of stay for CHF patients[17] with the average number of hospitalisations seen in placebo patients in the FAIR-HF trial and, for patients in the FCM group, with the proportional length of stay in the FCM arm (average length of stay across all patients and hospitalizations in the FCM group divided by average length of stay in the placebo group). For patients remaining hospitalised after 24 weeks an artificial discharge date (baseline plus 24 weeks) was assumed.

In the second, NYHA class-based approach to cost estimation, CHF-related medical resource use (other than for FCM and FCM administration) was assumed to be represented by the typical cost of a patient falling into a given NYHA class: cost proportions observed for CHF patients in different NYHA classes published by Levin and Szucs[18, 19] were multiplied with published total costs for CHF patients[20] and patient days per NYHA class according to data from the FAIR-HF study arms.

*Unit costs*. Costs for a hospital day for CHF patients were calculated using 2008-2009 NHS reference costs[21] (Table 2). For FCM, the UK purchasing price (PP) was used in the base case analysis.[22] Ambulatory administration costs were calculated using information on wages from the Personal Social Services Research Unit (PSSRU) data on unit costs for medical services.[15] Costs of materials were taken into account according to information from the Falkirk & District Royal Infirmary.[16]

Table 2. Model input parameters, ranges of variation and distribution type in sensitivity analysis.

| **Resource use** | **Unit** | **Value** | | **Range of variation in deterministic sensitivity analysis** | **Distribution type in probabilistic sensitivity analysis** |
|---|---|---|---|---|---|
| Mean dose of FCM received per patient[6]* | Mg | 1'851.33 | | 1'802.12–1'900.54 | Normal |
| Mean number of push injections (200mg) in FCM arm[6]* | - | 9.46 | | 9.21–9.72 | Normal |
| UK Hospital length of stay for CHF[17] | Days | 11.8 | | 8.26–15.34 | Triangular |
| Relative length of stay in FAIR-HF in FCM arm relative to Placebo arm †[6] | - | 0.36 | | 0.16-0.88 § | Lognormal |
| Length of stay per hospitalisation ‡[6] | Days | No iron: 2.95 | FCM: 1.07 | - | - |
| Frequency of hospitalisations ‡[6] | - | No iron: 0.17 | FCM: 0.08 | - | - |
| **Unit cost** | **Unit** | **Value** | | | |
| **FCM costs** | | | | | |
| Costs FCM (PP; per 100mg)[22] | € (£) | 21.20 (19.10) | | 18.03 †† (16.24) | - |
| **Administration costs** | | | | | |
| Push injection (wages & material)[15, 16] | € (£) | 22.36 (20.14) | | 15.64-29.06 (14.09–26.18) | Triangular |
| Costs per hospital day for CHF[21] | € (£) | 347.27 (312.86) | | 243.09-452.57 (219.00–407.72) | Triangular |
| **Other variables used in sensitivity analysis** | **Unit** | **Value** | | | |
| QALY-difference between arms ** | - | 0.037 | | 0.02–0.06 § | Normal |
| Data presented are rounded values. | | | | | |

*Due to missing data seven patients were excluded from summary statistics

† Cumulative over the study period

‡ Represented in the model by the combined parameter "relative length of stay in FAIR-HF"

§ Bootstrap-based confidence intervals

** QALY-difference as a clinical study endpoint is shown here because it was used for PSA

†† Used in scenario analysis

€, Euros; £, British Pounds; CHF, chronic heart failure; FCM, ferric carboxymaltose; Mg, milligram; PP, purchasing price; QALY, quality-adjusted life year; UK, United Kingdom

**Sensitivity analysis**

In order to assess the impact of statistical uncertainty around key model inputs, we performed a series of univariate and probabilistic sensitivity analysis.

*Univariate sensitivity analysis.* In univariate sensitivity analysis, we (1) varied the mean duration of hospitalisations for CHF in the UK and (2) the cost of a hospital day by ±30% and (3) drug costs by ±10% as no confidence intervals were available for these parameters. We further varied (4) QALY-difference, (5) proportional reduction of hospitalisation days and (6) frequency of hospitalisation in the placebo group on the basis of their confidence intervals. Further variations: (7) Calculation of results considering only cases with complete data on utilities, (8) calculation of costs via the NYHA class approach and (9) calculation of utilities using EQ-5D VAS scale scores.

*Probabilistic sensitivity analyses.* Probabilistic sensitivity analysis (second-order Monte Carlo simulation; PSA) was based on distributions corresponding to the ranges of variation used in the univariate sensitivity analyses assessing the impact of parameter uncertainty (Table 2). PSA was based on 10'000 sets of randomly drawn input parameters.

*Technical implementation.* The model was implemented and all Monte Carlo analyses were performed using TreeAge Pro 2011 Suite (TreeAge Software Inc., Williamstown, MA, USA). Further analyses were performed using Stata/IC 11 (StataCorp LP, College Station, TX, USA).

## RESULTS

### Characteristics of the study patients

The clinical characteristics of the FAIR-HF ITT population are presented in Table 1. At baseline, there were 53 patients (17.4%) in NYHA functional class II and 251 (82.6%) in class III in the treatment group, and 29 patients (18.7%) in class II and 126 (81.3%) in class III in the placebo group.

### Cost-effectiveness of i.v. iron therapy

In the base case analysis, mean QALYs were higher in the FCM arm (Placebo: 0.298; FCM 0.336); the difference was 0.037 QALYs (bootstrap-based 95% confidence interval [CI] 0.017–0.060) (Cost and cost-effectiveness results are shown in Table 3). The ICER of FCM compared to placebo, was €4’414 (£3’977) per QALY gained for the FAIR-HF dosing regimen. The FCM group yielded total costs of €852 (£768) and the placebo group of €687 (£619) over the study period. There were costs of €393 (£354) for the drug and €211 (£190) for administration compared to no costs on the placebo side. On the other hand, treatment with FCM saved €438 (£395) of costs for hospital treatment (FCM: €249 [£224]; Placebo: €687 [£619]) resulting in a net cost of the FCM strategy of €165 (£149) over 24 weeks.

Table 3. Overview of different approaches to analysis and results

| **Calculation in Base case analysis** | | | **Cost difference € (£) *** | **QALY difference** | **ICER € (£)** |
|---|---|---|---|---|---|
| • Cost via hospital days<br>• EQ-5D Questionnaire derived scores<br>• All cases (LOCF) | | | 165 (149) | 0.037 | 4'414 (3'977) |
| **Univariate sensitivity analysis** | | | | | |
| **Topic** | **Variable** | **Variation** | **Cost difference € (£) *** | **QALY difference** | **ICER € (£)** |
| **Costs** | Cost of a hospital day varied by | -30% | 297 (268) | 0.037 | 7'919 (7'134) |
| | | +30% | 34 (31) | | 905 (815) |
| | Cost of an ambulatory injection | -30% | 102 (92) | | 2'722 (2'452) |
| | | +30% | 229 (206) | | 6'108 (5'503) |
| | Calculation of costs via NYHA class approach | according to [19] | 528 (476) | | 14'096<br>14'582(12'699) |
| | | according to [18] | 546 (492) | | 14'582<br>(13'137) |
| | Drug costs varied by | -10% | 127 (114) | | 3'368 (3'034) |
| | | +10% | 204 (184) | | 5'462 (4'921) |
| **Resources** | Duration of hospitalisation for CHF in the UK | -30% | 297 (268) | | 7'925 (7'140) |
| | | +30% | 34 (31) | | 905 (815) |
| | Proportional reduction of hospitalisation days | lower margin of CI | 23 (21) | | 616 (555) |
| | | upper margin of CI | 519 (468) | | 13'855<br>(12'482) |
| | Frequency of hospitalisation in placebo group | lower margin of CI | 316 (285) | | 8'443 (7'606) |
| | | upper margin of CI | -39 (-35) | | FCM dominant |
| | Mean dose of FCM received per patient | lower margin of CI | 155 (140) | | 4'136 (3'726) |
| | | upper margin of CI | 175 (158) | | 4'693 (4'228) |
| | Mean number of push injections in FCM arm | lower margin of CI | 160 (144) | | 4'264 (3'841) |
| | | upper margin of CI | 171 (154) | | 4'565 (4'113) |

| | | | | | |
|---|---|---|---|---|---|
| **Utilities** | QALY-difference | lower margin of CI | 165 (149) | 0.017 | 9'673 (8'714) |
| | | upper margin of CI | | 0.060 | 2'738 (2'467) |
| | QALYs | complete records only | | 0.039 | 4'208 (3'791) |
| | Computation of utilities | VAS scale derived scores | | 0.023 | 7'201 (6'487) |

Data shown are cost difference (£), QALY difference and resulting ICER (£) of base case analysis and sensitivity analyses.

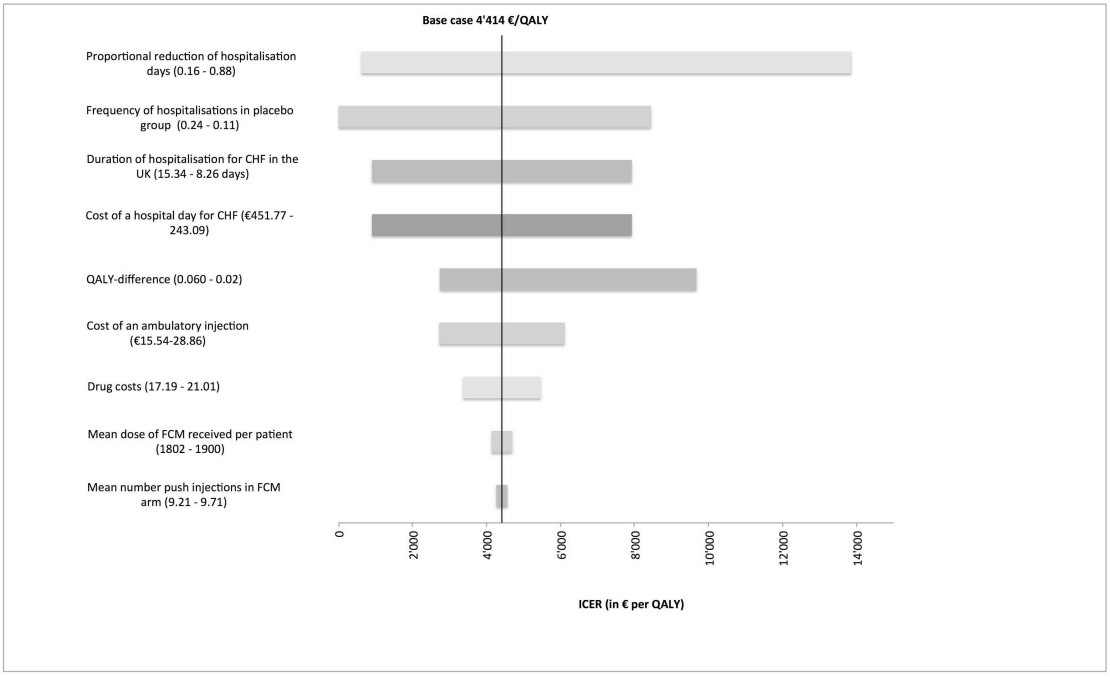
* positive numbers indicate FCM more expensive than placebo

€, Euros; £, British Pounds; CHF, chronic heart failure; CI, confidence interval; FCM, ferric carboxymaltose; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; NYHA, New York Heart Association; QALY, quality-adjusted life year; UK, United Kingdom; VAS, visual analogue scale

**Sensitivity analysis**

Univariate sensitivity analysis was carried out to characterise robustness of the base case results. Results ranged from dominance (i.e. being both cost-saving and more effective) of the i.v. iron strategy (€1045 [£941] saved; effectiveness 0.037 QALYs) to €13'855 (£12'482) per QALY gained. Frequency and duration of hospitalisation, QALY-difference and cost of a hospital day were the most influential parameters. Univariate sensitivity analysis results are presented in Table 3 and summarized in a Tornado diagram (Figure 1).

Figure 1. Tornado diagram of deterministic sensitivity analyses addressing the impact of parameter uncertainty (€, Euros; CHF, chronic heart failure; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UK, United Kingdom).




Analysis of mean days spent in each NYHA class, for FCM (placebo), resulted in 6.5 days (1) for NYHA class I, 58 days (40) for NYHA class II, 100 days (119) for NYHA class III and <1 day (3) for NYHA class IV. The approach of assessing CHF treatment costs based on the time spent in each NYHA class, resulted in costs of €1'907 (£1'718) for FCM and €1'361 (£1'226) for Placebo with a cost difference of €546 (£492) and a resulting ICER of €14'582 (£13'137), if the proportions according to Levin [18] were used. If the distribution according to Szucs [19] was used, costs were €1'415 (£1'275) for FCM and €887 (£799) for placebo with a cost difference of €528 (£476) and a resulting ICER of €14'096 (£12'699). None of the parameters tested resulted in an ICER less favourable than €22'200-33'300/QALY gained (£20'000-30'000), the threshold usually regarded as acceptable by the UK National Institute for Health and Clinical Excellence (NICE).[23]

PSA results showed mean costs of €877 (£790) for FCM and €686 (£618) for Placebo (range, FCM: €608-2050 [£548-1’847], Placebo: €369-1112 [£332-1’002]) and a mean effect of 0.038 QALYs (range -0.006-0.085). 9’866 scenarios (98.66%) were better than €22’200; 9’968 scenarios (99.68%) were better than €33’300. A cost-effectiveness scatterplot and cost-effectiveness acceptability curve are shown in Figure 2 and Figure 3, respectively. Generally, sensitivity analyses showed the results to be robust.

Figure 2. Cost-effectiveness scatterplot of 10’000 bootstrap replicates for incremental cost and incremental effectiveness. The circle is depicting 95% of observations. For each simulation run (represented as a dot), parameters were simultaneously and randomly sampled from the probability, cost, and outcome distributions for each strategy, to account for uncertainty in the base case parameter estimates. All simulation results fell in two quadrants of the cost-effectiveness plain: quadrant I (upper right), where the FCM strategy was both more costly and more effective than placebo, or quadrant II (lower right), where the FCM strategy was less costly and more effective (€, Euros; FCM, ferric carboxymaltose; QALYs, quality-adjusted life years).

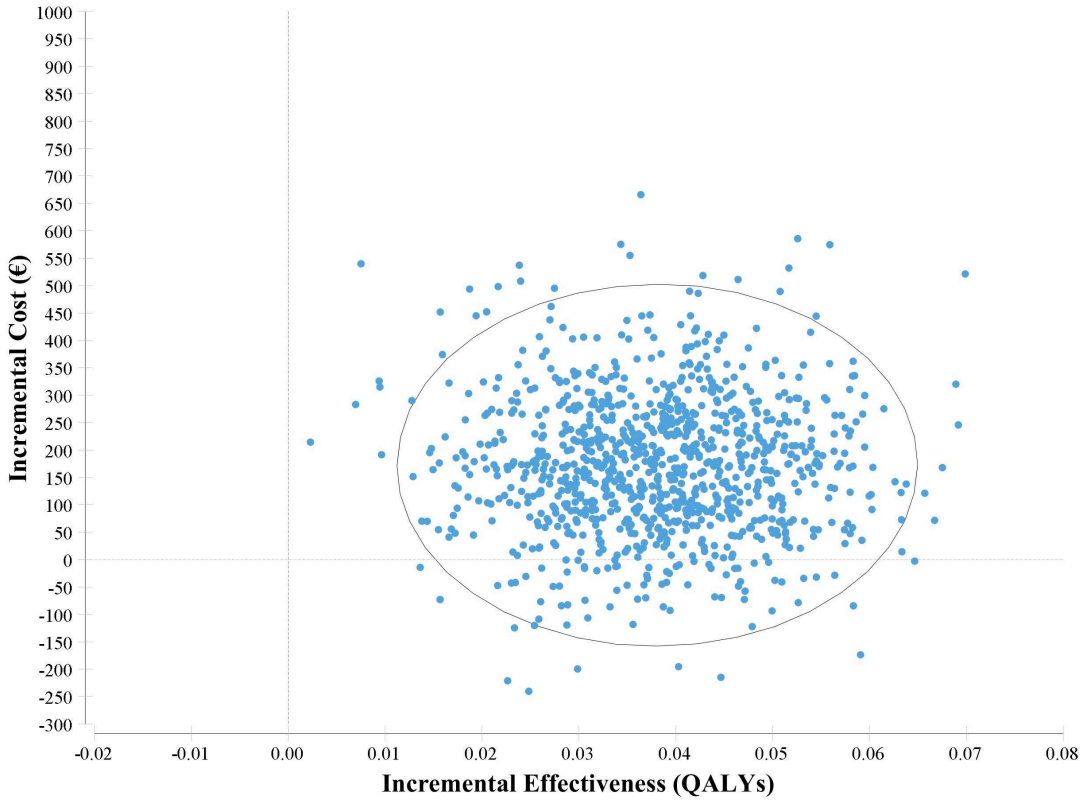
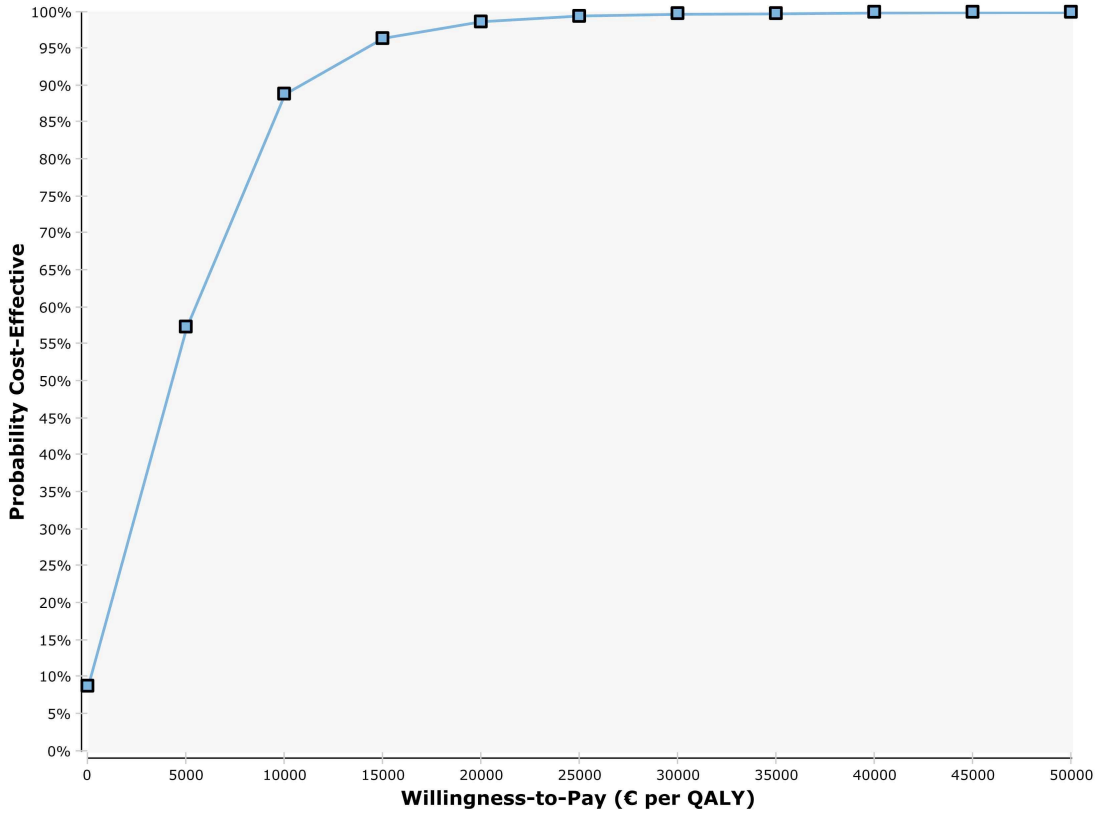


Figure 3. For different willingness-to-pay values, the cost effectiveness acceptability curve (CEAC) shows the probability that the FCM strategy (blue line) is cost-effective compared to Placebo The willingness-to-pay can be interpreted as the maximum amount one would be willing to pay for a gain of one quality-adjusted year of life (€, Euros; QALY, quality-adjusted life year).




## DISCUSSION

As the cost burden of CHF reaches up to 1-2% of health care budgets, cost-effective treatments to improve symptoms and QoL are needed.[24] The cost effectiveness of iron repletion using FCM, compared to no iron treatment, in CHF patients with iron deficiency derived from our trial-based analysis (€4'414/QALY gained in the base case) was distinctly below the cost-effectiveness threshold typically regarded as acceptable by NICE, of €22'200-33'300/QALY gained.[23] Mean QALYs were higher in the FCM arm and improved symptoms and better quality of life contributed to economic benefits seen with FCM. Sensitivity analyses showed ranges of QALY

differences (ICERs) from 0.017-0.060 (FCM dominant – €13'855) for the univariate and QALYs of -0.006-0.085 for the probabilistic analysis.

To the authors knowledge FAIR-HF is the first study that compared FCM to placebo in a population of CHF patients with iron deficiency. Clinical implications of FCM use compared to other i.v. and oral iron compounds have been studied in various indications. Cost-effectiveness analyses of FCM use are scarce across indications and none are available for CHF patients.

The use of ESAs in CHF patients is still under debate and further research is needed in this regard.[5] If ESA treatment was established as a therapeutic option, combination treatment with i.v. iron might have less cost implications in the long run than ESA treatment alone, as required ESA doses might be reduced.[25-29]

One important limitation of the present analysis is the lack of exhaustive medical resource use information; data on some uses of medical resources such as co-medications, devices (e.g. pacemakers) and ambulatory treatments could not be accounted for in the analysis, as they were not recorded in the FAIR-HF trial. As there is no indication of an increased use of unmeasured resource items in patients treated with i.v. iron versus patients with no iron treatment, the authors do not expect that other resource items, had they been included in the analysis, would diminish the cost difference between FCM and Placebo. The strategy to assess treatment costs via hospital days is likely to produce conservative results, because other potential resource savings relating e.g. to outpatient visits were not included in the calculation. In an alternative approach to cost assessment, treatment costs for CHF patients were estimated using the time spent in each NYHA class, and resulted in ICERs that are almost threefold compared to the approach of using hospital days to estimate costs.

Although the level of health care expenditure has been shown to be associated with NYHA class, this approach apparently cannot appropriately reflect changes in hospitalisation rate and duration, as observed in FAIR-HF. Moreover, clinical treatment regimens most likely will not immediately follow and be adapted to changes in NYHA class (particularly improvements), preventing a rapid translation into cost changes. While it is of interest to study the distribution of CHF costs across NYHA classes, reverse use of such information to predict costs in other situations does not appear to be a suitable option. The study by Szucs et al.[19] is based on a random sample of CHF outpatients Switzerland whereas the study by Levin et al. is based on the CHARM-trial[30], which contains data from CHF patients in 26 countries; both studies date back to 1999.

Some model inputs used in this analysis were subject to substantial uncertainty. It may e.g. be questionable whether NHS reported Healthcare Resource Group (HRG) costs really reflect actual hospitalisation costs. In the NYHA-based analysis, the most uncertain variable represented UK yearly costs for CHF treatment.

When discussing the generalizability of the presented results, it has to be noted that in routine clinical practice, fewer FCM administrations may be required, as FCM allows injections or infusions of up to 1,000 mg in 15 minutes, which may lead to improved ICERs. The extent to which this dosing regime may be achieved remains uncertain. Our analysis was based on average hospitalisation rates and lengths of stay. In routine practice, wide value ranges may occur and resource use may be structured differently which could lead to an under- or overestimation of costs.

The effect of FCM was seen in a closely followed patient group with high NYHA classes (roughly 20% NYHA II and 80% NYHA III) and may be different in other collectives. Compared to a UK routine practice population the FAIR-HF population

was older, consisted of more females, had lower diastolic and systolic blood pressure and higher comorbidity.[31] The impact of such differences is not currently predictable. Results of FAIR-HF stem from mostly pan-European study sites. There were no sites in the UK, but given the large European contribution one can assume that transferability of results to the UK is not substantially affected by geographical clinical variation. An analysis of anaemic vs. non-anaemic subgroups was not performed, as sample sizes would have been inadequate to perform a reliable analysis.

Study data cover a period of 24 weeks of treatment. Extrapolation of the time horizon to a longer term, e.g. lifelong time horizon, was not considered adequate as the FAIR-HF trial provides no information on long-term survival or other long-term effects. The cost-effectiveness of longer-term iron treatment remains unknown.

Given that the trial only collected very limited resource use data the results do have an approximate character to some extent. In order to gain more in depth knowledge about use of FCM in CHF patients, e.g. whether treatment and cost effects sustain over a longer period, trials covering longer time periods and gathering further resource use should be in the focus of further research. In conclusion it can be noted that over the study period, treatment with FCM in iron-deficient CHF patients with or without anaemia improves symptoms and is likely to be cost effective in routine clinical practice, from the perspective of the UK NHS.

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**CONFLICT OF INTEREST:**

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**APPENDIX I**

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